

# **Genetic Mapping: genome-wide association analysis**

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Genotypic risk ratio	Frequency of disease allele	Number of singletons required
4.0	0.01	1098
	0.10	150
	0.50	103
	0.80	222
2.0	0.01	5823
	0.10	695
	0.50	340
	0.80	640
1.5	0.01	19,320
	0.10	2218
	0.50	949
	0.80	1663

Assuming 100,000 comparisons  
(Risch et al. Science 273:1516-17, 1996)

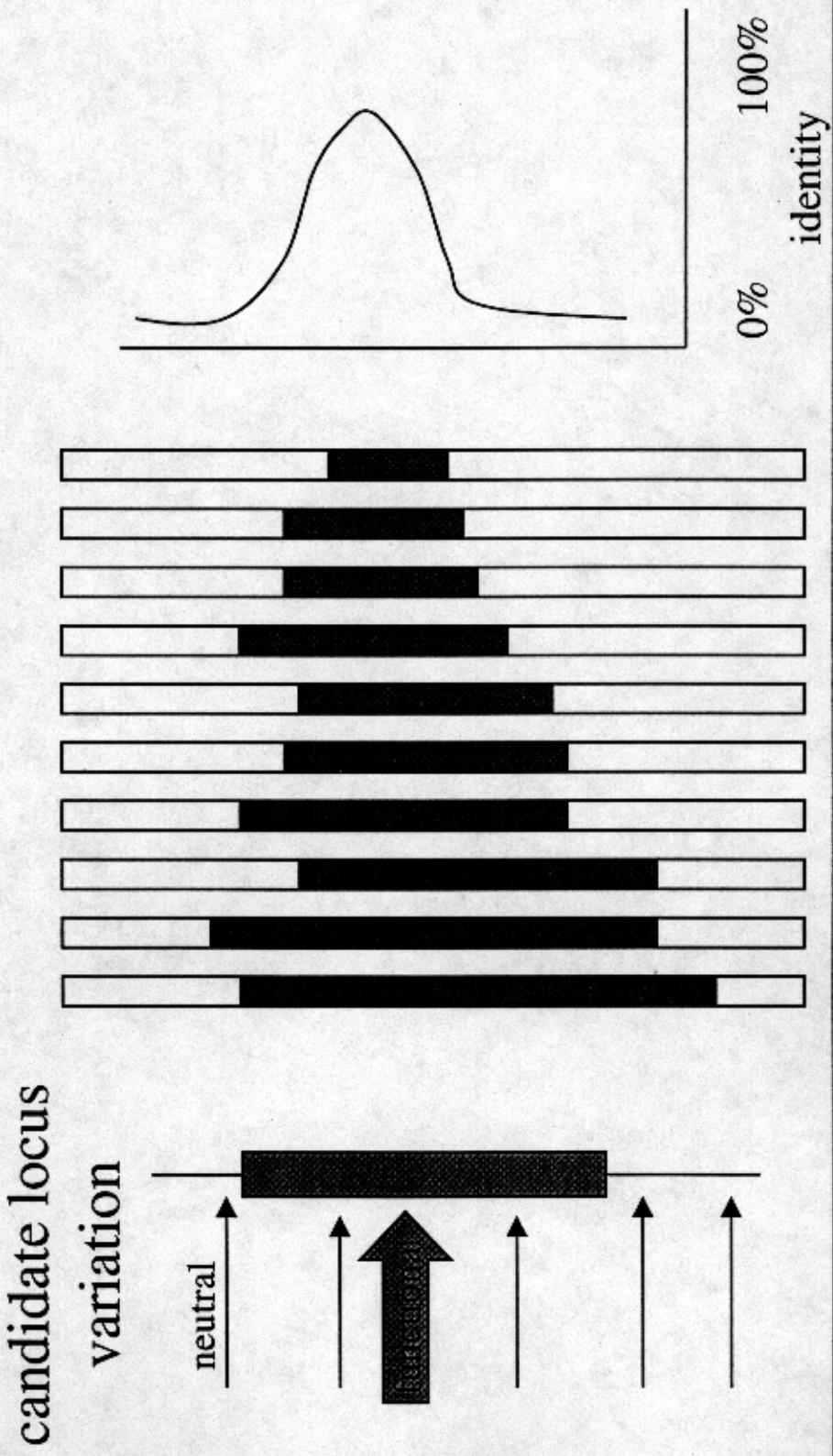
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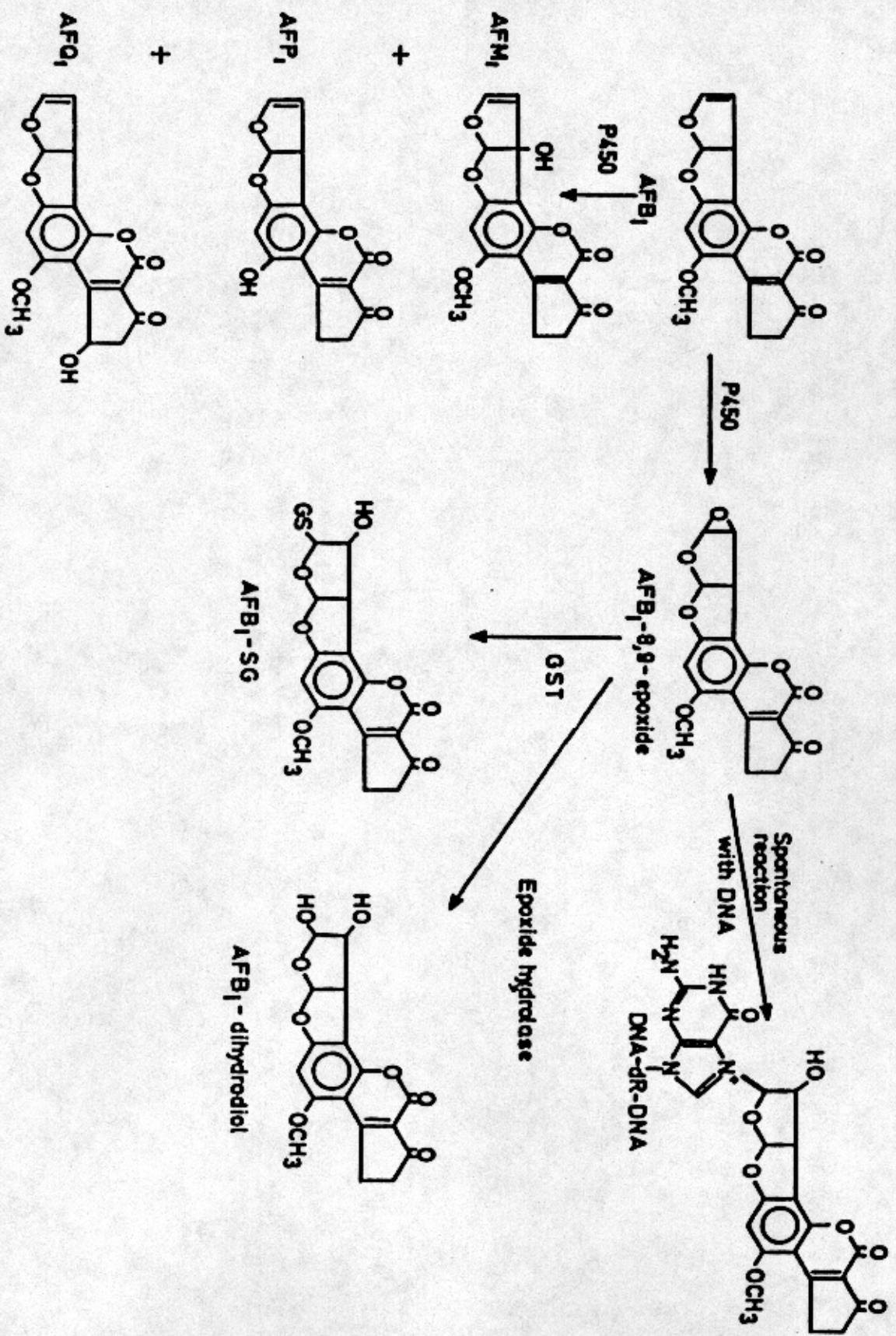
# Using intra-locus linkage disequilibrium to identify functionally significant candidate locus variation



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**Metabolism of aflatoxin B<sub>1</sub> by cytochrome P450  
glutathione S-transferase and epoxide hydrolase**



# Genetic Mapping: pathway dissection by association analysis

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size of effect	number of tests			
	1	2	5	10
<b>1.5</b>	153	195	250	291
<b>2.0</b>	55	69	89	104
<b>4.0</b>	16	21	27	31

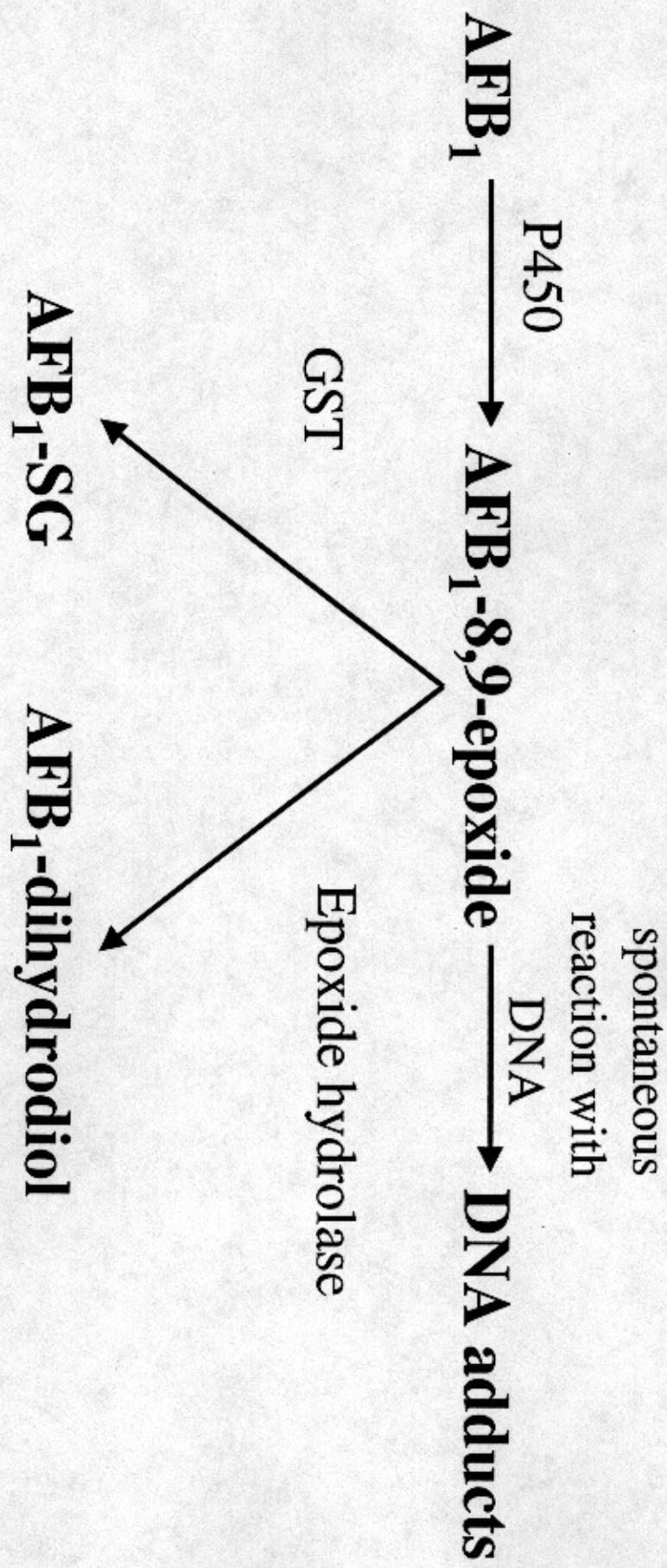
(Risch et al. Science 273:1516-17, 1996)



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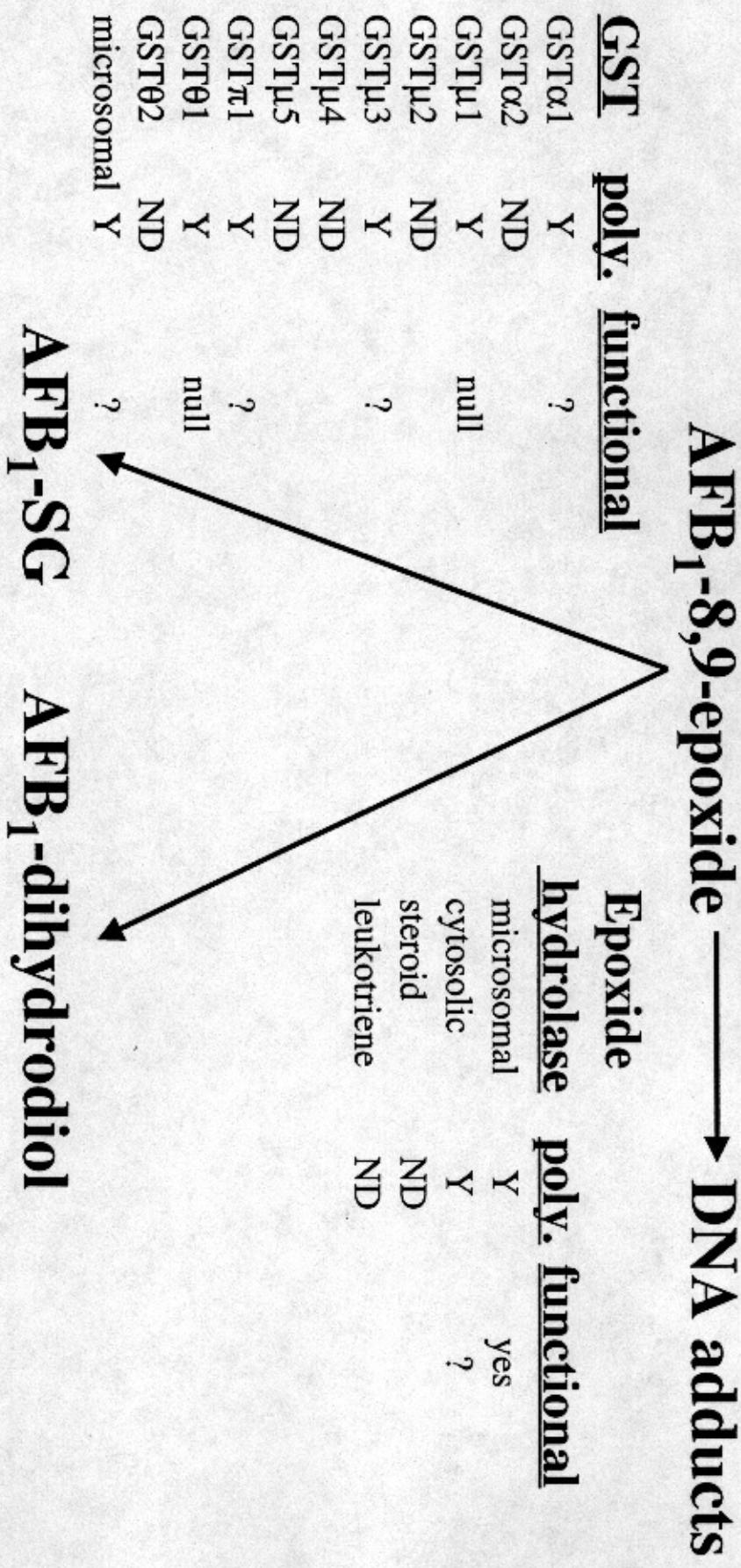
# Metabolism of aflatoxin B<sub>1</sub> by cytochrome P450, glutathione S-transferase and epoxide hydrolase



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# glutathione S-transferase and epoxide hydrolase gene families and associated variation profiles



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# glutathione S-transferase and epoxide hydrolase variation and primary hepatocellular carcinoma (HCC) risk

$\text{AFB}_1\text{-8,9-epoxide} \longrightarrow \text{DNA adducts}$

<u>GST</u>	<u>poly.</u>	<u>HCC risk</u>	<u>Epoxide</u>	<u>hydrolase</u>	<u>poly.</u>	<u>HCC risk</u>
GST $\alpha$ 1	Y	ns	microsomal	Y	yes	
GST $\mu$ 1	Y	yes	cytosolic	Y	yes	
GST $\mu$ 3	Y	ns				
GST $\pi$ 1	Y	yes				
GST $\theta$ 1	Y	yes				
microsomal	Y	ns				



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# Genetic Analysis

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- ◆ family studies
- ◆ population definition
- ◆ pathway dissection
- ◆ genome-wide association studies



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# **Human Genetic Mapping**

## **Electronic Address List**

### **General**

<http://linkage.cpmc.columbia.edu>

<http://lenti.med.umn.edu/linkage/linkage.html>

### **Reference Maps and Data**

<http://www.chlc.org>

[http://gopher.genethon.fr/genethon\\_en.html](http://gopher.genethon.fr/genethon_en.html)

<http://www.cephb.fr>

<http://www.ncbi.nlm.nih.gov>

<http://gdbwww.gdb.org>

### **Trait Mapping Software**

#### **LINKAGE ANALYSIS (comprehensive)**

<http://linkage.cpmc.columbia.edu/software.html>

#### **FASTLINK version of LINKAGE PACKAGE**

<http://www.cs.rice.edu/~scaffer/fastlink.html>

#### **HETEROGENEITY ANALYSIS**

<ftp://linkage.cpmc.columbia.edu/software/homog>

#### **APM ANALYSIS**

<ftp://watson.hgen.pitt.edu/pub>

#### **LINKAGE DISEQUILIBRIUM**

<ftp://linkage.cpmc.columbia.edu/software/diseq>

#### **SIMLINK SOFTWARE (for power calculations)**

<http://www.sph.umich.edu/group/statgen/software>